Thiol–ene Click Hydrogels for Therapeutic Delivery

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Authors: Prathamesh M Kharkar, Matthew S Rehmann, Kelsi M Skeens, Emanual Maverakis, April M Kloxin

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Public Summary:
Hydrogels are of growing interest for the delivery of therapeutics to specific sites in the body. For use as a delivery vehicle, hydrophilic precursors are usually laden with bioactive moieties and then directly injected to the site of interest for in situ gel formation and controlled release dictated by precursor design. Hydrogels formed by thiol–ene click reactions are attractive for local controlled release of therapeutics owing to their rapid reaction rate and efficiency under mild aqueous conditions, enabling in situ formation of gels with tunable properties often responsive to environmental cues. Herein, we will review the wide range of applications for thiol–ene hydrogels, from the prolonged release of anti-inflammatory drugs in the spine to the release of protein-based therapeutics in response to cell-secreted enzymes, with a focus on their clinical relevance. We will also provide a brief overview of thiol–ene click chemistry and discuss the available alkene chemistries pertinent to macromolecule functionalization and hydrogel formation. These chemistries include functional groups susceptible to Michael type reactions relevant for injection and radically mediated reactions for greater temporal control of formation at sites of interest using light. Additionally, mechanisms for the encapsulation and controlled release of therapeutic cargoes are reviewed, including (i) tuning the mesh size of the hydrogel initially and temporally for cargo entrapment and release and (ii) covalent tethering of the cargo with degradable linkers or affinity binding sequences to mediate release. Finally, myriad thiol–ene hydrogels and their specific applications also are discussed to give a sampling of the current and future utilization of this chemistry for delivery of therapeutics, such as small molecule drugs, peptides, and biologics.

Scientific Abstract:
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